

REMARKS/ARGUMENTS

With this amendment, claims 1, 2, 13, 25 and 26 are pending in the present application. Claim 25 has been amended to refer only to treating cardio-cerebral ischemic diseases. No new matter is added by these amendments.

Rejections under 35 U.S.C. §112, first paragraph

Claims 25 and 26 stand rejected for allegedly lacking enablement. The Examiner acknowledges that the specification enables treatment of cardio-cerebral ischemic diseases, but alleges that it does not enable prevention of such diseases. To expedite prosecution, claim 25 has been amended to delete reference to prevention of disease. Applicants note, however, that rejected claims are composition claims, not method claims. Thus, the claims are fully enabled, so long as a single use is enabled. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103(a)

Claims 1-2, 13, and 25-26 stand rejected for allegedly being obvious over Yang *et al.*, (CN 1382682, equivalent to US 2005/0288263) in view of Berge *et al.*, *J. Pharm Sci* 66:1-19 (1977)). In the Office Action, the Examiner asserts that it would have been obvious to formulate the sodium salt of 2-(α -n-pentanonyl)benzoate (which is taught in STN Registry No. 550-37-8) based on the teaching in Yang *et al.* of the compound, 2-(α -hydroxypentyl)benzoate, in view of the teaching by Berge *et al.*, that sodium is a potentially useful salt form that is approved by the FDA.

As noted by the Examiner, an analysis of obviousness requires, among other things, a determination of the scope and content of the prior art. Such a determination requires that the cited prior art be considered *in its entirety*, including disclosures that teach away from the claimed invention. See MPEP § 2141.03 VI. As explained below, a careful reading of Yang *et al.*, reveals that it actually teaches away from the use of sodium salts, at least for the compound disclosed there.

As noted by the Examiner, Yang *et al.*, discloses, among other salts, the sodium salt of 2-(α -hydroxypentyl)benzoate. However, Yang *et al.* disclose that the preferred salt for hydroxypentyl compound is *potassium*, not sodium. As shown in examples 5, 6, 7 and 8 of

Yang *et al.*, the sodium salt is a sticky, yellow substance, which can only form a white amorphous foam, even after further treatment. This result is contrasted with the totally different results obtained with the potassium salt (*see* examples 1, 2, 3 and 4) that produced a white particulate crystal with a melting point of 151-152°C. Indeed, Yang *et al.* selected the potassium salt as the preferred salt for further experiments demonstrating the therapeutic effects of the compound disclosed there (*see* examples 16 and 17). As a result, one of skill considering the art *in its entirety* would have considered the Yang *et al.*, disclosure to teach away from the use of the sodium salt in view of the relatively poor results compared to the potassium salt.

In addition, the results of Yang *et al.*, demonstrate the general unpredictability of forming salts of the claimed compound. It is well settled that in order to establish a *prima facie* case of obviousness, the Examiner must show that one of skill would have had a reasonable expectation of success. MPEP §2143.02. As explained below, based on the unpredictability of the art, one of skill could not have reasonably predicted that sodium would be a useful salt of the claimed compounds.

The STN document cited by examiner discloses the free acid 2-(α -n-pentanonyl)benzoic acid. As disclosed in example 1 of the present application, 2-(α -n-pentanonyl)benzoic acid is a yellowish colloidal solid after the solvent is removed. A person skilled in the art would recognize that if a colloidal solid is obtained after evaporating the solvent, the substance is an amorphous one, which is hard to collect and preserve. For example, the solvent residue in a colloidal solid cannot be totally removed, and the amount of the solvent as well as the form of the solid can vary. Moreover, as 2-(α -n-pentanonyl)benzoic acid cannot be purified by recrystallization, in practice, it is difficult to obtain a high quality pure compound.

More importantly, a person skilled in the art knows that even different salts of a same compound have totally different properties. Indeed, Yang *et al.* demonstrates the stark differences between the sodium and potassium salts of the hydroxypentyl compound disclosed there. Thus, it is unreasonable for a person skilled in the art to predict a particularly selected salt, sodium 2-(α -n-pentanonyl)benzoate would have the good properties demonstrated here, merely based on an acid, 2-(α -n-pentanonyl)benzoic acid, disclosed in the STN document.

Moreover, Berge *et al.*, which the Examiner relies on to support the present rejection, actually provides further evidence of the lack of predictability in this art. Berge *et al.* teaches that “the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and hence often optimized by conversion to a salt form” and lists many salts, such as Al, Ca, Li, Mg, K, Na, Zn and the like, that can be used. However, Berge *et al.*, also clearly teaches in the 1st paragraph, right column, on the first page, that “salt-forming agents are *often chosen empirically*. Of the many salts synthesized, the preferred form is selected by pharmaceutical chemists primarily on a practical basis... Unfortunately, *there is no reliable way of predicting* the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility and formulation profiles”. (emphasis added).

Thus, although Berge *et al.*, teaches that an acid can be converted to a salt form, it is clear that the properties of a particular salt cannot be predicted, even after many salts of the same basic agent have been prepared. Thus, the prior art as a whole demonstrates that one of skill would not have a reasonable expectation of success in selecting sodium 2-(α -n-pentanonyl)benzoate as claimed here.

Finally, in analyzing obviousness, the Examiner must also consider evidence of surprising or unexpected results of the claimed invention. MPEP §2145. As demonstrated in the specification, sodium 2-(α -n-pentanonyl)benzoate has surprisingly good properties, as compared to other salts.

The present application, for example, at paragraph [0011], discloses that the selection of the sodium salt was based on preparing and studying a large number of 2-alkyl benzoates including organic and inorganic salt, and comparing various properties, such as the purity, the structure, the stability, the solubility, and effects thereof.

As disclosed in paragraph [0023] of the present application, sodium 2-(α -n-pentanonyl)benzoate is a white powdered crystal with good stability and high melting point of 219-220°C. The present application further demonstrates to a person skilled in the art that the

claimed compound has good process ability such as flow ability, compressibility, comminuting ability and the like.

Table 1 on page 15 of the present application shows that the sodium salt of the present invention has a very good stability; even compared to the preferred potassium salt of the hydroxypentyl compound of Yang *et al.* Examples 13 to 15 disclose the stability to humidity, stability to light, and thermal stability of the present sodium salt. Example 21 also shows that acute toxicity of the present sodium salt is lower than that of the sodium salt of the compound described in Yang *et al.*

Additionally, examples 22 and 23 of the present invention clearly set forth the surprisingly good pharmacology effects of the claimed sodium salt. For example, the cerebral infarct of rats in the group of sodium salt was significantly reduced as compared with the Model group (*see* paragraph [0121] of the present application), and the maximum % inhibition of sodium 2-(α -n-pentanonyl)benzoate was up to 45.39% and 48.16% respectively (*see* paragraph [0120] of the present application).

In conclusion, the prior art when considered in its entirety actually teaches away from sodium 2-(α -n-pentanonyl)benzoate because Yang *et al.*, teaches that, for the hydroxypentyl compound, the potassium salt is preferred over the sodium salt. In addition, the prior art also shows that the properties of any particular salt are unpredictable and that one of skill would have lacked a reasonable expectation of success in choosing the sodium salt. Finally, the sodium salt has surprisingly good properties as compared to other salts. In view of all of the above, the rejection of the claims is improper. Withdrawal of the rejection is respectfully requested.

Appl. No. 10/598826
Amdt. dated December 23, 2008
Reply to Office Action of September 24, 2008

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

/Kevin Bastian/

Kevin Bastian
Reg. No. 34,774

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
KLB:klb
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